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(54) Title: NOVEL MEDICAL USE OF SELECTIVE CB_1-RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to a novel medical use of selective CB_1 receptor antagonistic compounds. Said compounds are particularly suitable in the manufacture of medicaments for the treatment and/or prophylaxis of CB_1 receptor related diseases in juvenile patients (pediatric treating), e.g. in particular obesity in juvenile patients, and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as in adolescent patients. The CB_1 receptor antagonistic compounds suitable according to the invention are elucidated in more detail in the description.

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SPH0319WO

Solvay Pharmaceuticals GmbH

NOVEL MEDICAL USE OF SELECTIVE CB1-RECEPTOR ANTAGONISTS

The present invention relates to novel therapeutic and/or prophylactic uses of selective CB_1-antagonists and to pharmaceutical compositions containing one or more of these compounds as an active component for the novel uses. The selective CB_1-antagonists addressed in this invention are potent Cannabis-1 (CB_1) receptor antagonists with outstanding utility for the novel medical uses provided by the present invention.

Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB_1 and CB_2) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB_1 receptors in the brain, in combination with the strictly peripheral localisation of the CB_2 receptor, makes the CB_1 receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* **1998**, 5, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458). Hitherto, three types of distinct CB_1 receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB_1 receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* **1994**, *5*, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M.; Moerschbaecher, J.M.; Barker, L.A. *CNS Drug Rev.* **1999**, *5*, 43). Aminoalkylindoles have been disclosed as CB_1 receptor antagonists. A

representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a CB_1 receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, *61*, PL115). More recently, researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB_1 receptor antagonists (*e.g.* LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H., Lambert, D.M. *Biorg. Med.Chem. Lett.* **1999**, *9*, 2233). Interestingly, many CB_1 receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, *334*, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, *359*, 1). From the international patent application WO 01/70700 4,5-dihydro-1H-pyrazole compounds are known which exhibit potent and selective cannabis CB_1-receptor antagonistic activity.

It is an objective of the invention to provide improved methods of treatment and/or prophylaxis which are particularly suitable in patient groups with enhanced need of safety and tolerability, e.g. in the treatment of obesity patients, in particular such as juvenile obesity patients and/or patients subject to long term treatment, e.g. in drug induced obesity in juvenile or adolescent patients.

It has now surprisingly been found that selective CB_1-antagonists in general, prodrugs thereof, tautomers thereof and salts thereof, show a unique pharmacological profile and therefore are particularly suited for the use in the manufacture of a medicaments for the treatment and/or prophylaxis of obesity patients, in particular of obesity in juvenile patients and/or drug induced obesity in juvenile, as well as adolescent, patients. In this regard selective CB_1-antagonistic compounds are highly valuable in providing medicaments for paediatric use on the one hand, and for the general use in drug induced obesity.

The term "selective" means that preferably there is no substantial other activity

than the CB_1-receptor antagonistic activity, or that at least the CB_1-receptor antagonistic activity is substantially overcompensating any other activity.

The outstanding unique pharmacological profile of selective CB_1-antagonistic compounds includes particularly high safety and tolerability which make the compounds particularly suitable in patient groups with enhanced need of safety and tolerability, in particular such as juvenile patients and/or patients subject to long term treatment, e.g. in drug induced obesity.

Due to the potent and selective CB_1 antagonistic activity the compounds used according to the invention are suitable also for use in paediatric treatment and/or prophylaxis of other disorders than juvenile obesity and drug induced obesity in juvenile patients. The other disorders include those known from the literature for the concerned selective CB_1 antagonistic compound, e.g. paediatric treatment and/or prophylaxis may pertain to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, neurological disorders such as dementia, distonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders, in young patients.

The whole content of the literature mentioned in the description of the present invention is incorporated by reference into the present application.

The selective CB_1 antagonistic compounds used in the present the invention can be obtained according to known methods. Suitable ways of synthesis for the compounds used according to the present invention are described in the state of the art, e.g. in the documents cited in the present application and incorporated by reference.

Examples of selective CB_1 antagonistic compounds being relevant in the context of the present invention and incorporated by reference are for example (but not being limited thereto):

1) Diarylpyrazole congeners disclosed by Sanofi as selective CB_1 receptor antagonists, e.g. as representative example the compound SR-141716A, rimonabant and related compounds described e.g. in EP 0969835, SR-147778, SR-140098 (Central mediation of the cannabinoid cue: activity of

a selective CB1 antagonist, SR 141716A Perio A, Rinaldi-Carmona M, Maruani J Behavioural Pharmacology 1996, 7:1 (65-71)); WIN-54461 disclosed by Sanofi-Winthrop (Cannabinoid receptor ligands : Clinical and neuropharmacological considerations relevant to future drug discovery and development. Pertwee RG, Expert Opinion on Investigational Drugs 1996, 5:10 (1245-1253))

2) Aminoalkylindoles having been disclosed as CB_1 receptor antagonists, e.g. as a representative example the compound Iodopravadoline (AM-630),

3) Aryl-aroyl substituted benzofurans described by Eli Lilly as selective CB_1 receptor antagonists, e.g.LY-320135 (Cannabinoid receptor ligands : Clinical and neuropharmacological considerations relevant to future drug discovery and development. Pertwee RG, Expert Opinion on Investigational Drugs 1996, 5:10 (1245-1253)),

4) Compounds described by Merck & Co, e.g. AM 251 and AM 281 (Conference: 31st Annual Meeting of the Society for Neuroscience, San Diego, USA, 10-15.11.2001), and substituted imidazolyl derivatives disclosed e.g. in US 2003-114495 or WO 03/007887,

5) Azetidine derivatives described by Aventis Pharma e.g. in WO 02/28346 or EP 1328269,

6) CP-55940 from Pfizer Inc. (Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors, Felder CC, Joyce KE, Briley EM, Mansouri J, Mackie K, Blond O, Lai Y, Ma AL, Mitchell RL, Molecular Pharmacology 1995, 48:3 (443)),

7) Diaryl-pyrazine-amide derivatives from Astra Zeneca described e.g. in the WO 03/051851,

8) ACPA and ACEA from Med. Coll. Wisconsin (Univ. Aberdeen), ("Effects of AM 251 & AM 281, cannabinoid CB1 antagonists, on palatable food intake in lewis rats" J.Pharmacol.Exp.Ther. 289, No3, 1427-33, 1999),

9) Pyrazole derivatives described by the University of Conneticut e.g. in the WO 01/29007,

10) HU-210 (International Association for the Study of Pain - Ninth World Congress (Part II) Vienna, Austria, Dickenson AH, Carpenter K, Suzuki R, IDDB MEETING REPORT 1999, August 22-27) and HU-243 (Cannabinoid receptor agonists and antagonists, Barth F, Current Opinion in Therapeutic Patents 1998, 8:3 (301-313)) from Yissum R&D Co Hebrew Univ. of Jerusalem,

11) O-823 from Organix Inc. (Drug development pipeline: O-585, O-823, O-689, O-1072, nonamines, Orgaix, Altropane Organix Inc, Company

Communication 1999, August 10; IDDb database) and O-2093 from Consiglio Nazionale delle Ricerche ("A structure/activity relationship study on arvanil, endocannabinoid and vanilloid hybrid.", Marzo DV, Griffin G, Petrocellis L, Brandi I, Bisogno T, Journal of Pharmacology and Experimental Therapeutics 2002, 300:3 (984-991)),

12) 3-Alkyl-5,5'-diphenylimidazolidinediones which were described as cannabinoid receptor ligands,

13) CB_1 antagonistic compounds currently under development by Bayer AG (IDDb database: company communication 2002, February 28).

The CB_1 antagonistic compounds used according to the invention can be brought into forms suitable for paediatric administration, as well as for the administration in treating drug induced obesity by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

Hence, in a further aspect the invention also pertains to a pharmaceutical composition containing at least one selective CB_1 antagonistic compound as an active component for the treatment and/or prophylaxis of CB_1 receptor related diseases in juvenile patients and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, and at least one auxiliary excipient. In such a pharmaceutical composition the selective CB_1 antagonistic compound is preferably present in an amount effectively suited for the treatment and/or prophylaxis of a psychiatric disorder, a gastrointestinal disorder, a cardiovascular disorder, or a combination of said disorders, in a juvenile patient in need of such treating.

In a further embodiment of the invention in the pharmaceutical composition the selective CB_1 antagonistic compound is present in an amount effectively suited for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients in need of such treating.

Finally the invention also includes a method of treatment and/or prophylaxis of CB_1 receptor related diseases in juvenile patients, in particular juvenile obesity, and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, characterized in that a compound of formula (I) is administered to said patient in need of such treating. The method of treatment and/or prophylaxis according to the invention may be further characterized in that it is a paediatric treating which is directed to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite

disorders, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischemia, pain and other CNS-diseases involving cannabinoid neurotransmission, in young patients.

Preferably, in one embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of obesity in juvenile patients. In another preferred embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of drug induced obesity in juvenile or adolescent patients. This drug induced obesity may be in particular caused by drugs like atypical antipsychotics.

In one embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of obesity in juvenile patients. Thus, it is advantageous that Cannabinoid antagonists are suitable for the treatment of Childhood Obesity and related Comorbidities as for example Type 2 Diabetes. There is a clear medical need for improved therapy as obesity has become an increasingly important medical problem not only in the adult population but increasingly in children and (young and older) adolescents. In national surveys from the 1960s to the 1990s in the United States, the prevalence of overweight in children grew from 5% to 11% (Sorof and Daniels 2002). In Canada as another example childhood obesity has tripled in the past 20 years (Spurgeon 2002). Obesity in childhood causes a wide range of serious complications, and increases the risk of premature illness and death later in life, raising public-health concerns (Ebbeling, Pawlak et al. 2002). Over the last decades a tremendous increase of cases of type 2 diabetes was observed, especially also in children. This epidemic trend is clearly reflecting the increasing rates of obesity. Type-2-diabetes was in the past considered a disease of adults and older individuals, not a paediatric condition (Arslanian 2002). One of the main risk factor of paediatric type 2 diabetes is obesity.

Type 2 diabetes in children (as is in adults) is part of the insulin resistance syndrome (Rosenbloom 2002) that includes hypertension, dyslipidemia and other atherosclerosis risk factors, and hyperandrogenism seen as premature adrenarche and polycystic ovary syndrome. Other outcomes related to childhood obesity include left ventricular hypertrophy, nonalcoholic steatohepatitis, obstructive sleep apnea, orthopedic problems, and severe psychosocial problems.

In addition primary hypertension has become increasingly common in children again associated obesity as a major independent risk factor. Obese children are at approximately a 3-fold higher risk for hypertension than non-obese children (Sorof and Daniels 2002). The benefits of weight loss for blood pressure reduction in children have been demonstrated in both observational and interventional studies.

Public concerns are rising because of a rapid development of the childhood obesity epidemic in genetically stable populations. Driving factors are assumed to be mainly adverse environmental factors for which straightforward recommendations of life style modifications exists. Obesity and it's related co-morbidities are very serious medical conditions and state of the art measures and treatment of obesity and especially childhood obesity remain largely ineffective at the time being (Ebbeling, Pawlak et al. 2002). The management of type 2 diabetes in is also especially difficult in children and the adolescent age group (Silink 2002). Craving for and over consumption of palatable food is one of the important factors of life-style related obesity in humans and especially also in children and adolescents. Treatment of type 2 diabetes and other co-morbid conditions by the degree of metabolic derangement and symptoms: The only data on the use of oral hypoglycemic agents in children with type 2 diabetes has been with metformin (Rosenbloom 2002).

Thus, CB_1 antagonists used according to the present invention offer a unique opportunity for the treatment of obesity by interacting with these "driving forces". They are superior to current medical treatments and especially suited for pediatric treatment because of their outstanding safety profile and/or tolerability. Treatment of obesity especially childhood obesity is besides efficacy dictated by safety.

Obesity in childhood is a medical condition that is likely to require long-term management. The safety profile of CB_1 antagonists according to the present invention are suggested to be superior to current standard medications, and these CB_1 antagonists will be especially suited for the treatment and prevention of childhood obesity and related co-morbidities.

Literature:

Arslanian, S. (2002). "Type 2 diabetes in children: clinical aspects and risk factors." Horm Res **57 Suppl 1**: 19-28.

Ebbeling, C. B., D. B. Pawlak, et al. (2002). "Childhood obesity: public-health crisis, common sense cure." Lancet **360**(9331): 473-82.

Rosenbloom, A. L. (2002). "Increasing incidence of type 2 diabetes in children and adolescents: treatment considerations." Paediatr Drugs 4(4): 209-21.

Silink, M. (2002). "Childhood diabetes: a global perspective." Horm Res **57 Suppl 1**: 1-5.

Sorof, J. and S. Daniels (2002). "Obesity hypertension in children: a problem of epidemic proportions." Hypertension **40(4)**: 441-7.

Spurgeon, D. (2002). "Childhood obesity in Canada has tripled in past 20 years." Bmj **324(7351)**: 1416.

In another embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of drug induced obesity in juvenile or adolescent patients. Drug induced weight gain is also of major concern and subject to high medical need of improved treatments. Again, in this context the CB_1 antagonists according to the present invention are suggested to be superior to current standard medications, and these CB_1 antagonists will be especially suited for the treatment and prevention of drug induced obesity in juvenile as well as in adolescent patients.

Regarding drug induced weight gain, it is reported by Zimmermann, U., T. Kraus, et al. (2003, "Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients." J Psychiatr Res 37(3): 193-220) that body weight gain frequently occurs during drug treatment of psychiatric disorders and is often accompanied by increased appetite or food craving. While occurrence and time course of this side effect are difficult to predict, it ultimately results in obesity and the morbidity associated therewith in a substantial part of patients, often causing them to discontinue treatment even if it is effective. Weight gain appears to be most prominent in patients treated with some of the second generation antipsychotic drugs and with some mood stabilizers. Marked weight gain also frequently occurs during treatment with most tricyclic antidepressants.

Very large weight gains are associated with drugs like for example the atypical antipsychotics clozapine and olanzapine. Some atypical antipsychotics, however, tend to cause significant weight gain, which may lead to poor compliance and other adverse health effects (Nasrallah, H. (2003). "A review of the effect of atypical antipsychotics on weight." Psychoneuroendocrinology 28 Suppl 1: 83-96.). The mechanisms involved in antipsychotic drug-related weight gain are as

yet uncertain, although serotoninergic, histaminic, and adrenergic affinities have been implicated along with other metabolic mechanisms. The atypical antipsychotics vary in their propensity to cause weight change with long-term treatment. Follow-up studies show that the largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when constructing an algorithm for treatment due to the serious medical consequences of obesity. In this regard co-administration of CB_1 antagonist according to the invention is suggested to work beneficially.

Claims

1. Use of a CB_1 receptor antagonistic compound, prodrugs thereof, tautomers thereof and salts thereof, in the manufacture of medicaments for the treatment and/or prophylaxis of CB_1 receptor related diseases in juvenile patients and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as in adolescent patients:

2. Use of a CB_1 receptor antagonistic compound according to claim 1, wherein the compound is selected from the group of

   14) Diarylpyrazole selective CB_1 receptor antagonists, preferably the compounds SR-141716A, rimonabant and related compounds, SR-147778, SR-140098 and/or WIN-54461;
   15) Aminoalkylindoles selective CB_1 receptor antagonists, preferably the compound Iodopravadoline (AM-630);
   16) Aryl-aroyl substituted benzofuran compounds with selective CB_1 receptor antagonistic activity, preferably the compound LY-320135;
   17) Selective CB_1 receptor antagonistic compounds AM251 and/or AM281, and substituted imidazolyl compounds with selective CB_1 receptor antagonistic activity;
   18) Azetidine derivatives with selective CB_1 receptor antagonistic activity;
   19) The compound CP-55940;
   20) Diaryl-pyrazine-amide with selective CB_1 receptor antagonistic activity;
   21) The compounds ACPA and ACEA;
   22) Pyrazole derivatives with selective CB_1 receptor antagonistic activity;
   23) The compounds HU-210 and/or HU-243;
   24) The compounds O-585, O-823, O-689, O-1072, and/or O-2093;
   25) 3-Alkyl-5,5'-diphenylimidazolidinediones with selective CB_1 receptor antagonistic activity
   26) CB_1 antagonistic compounds with selective CB_1 recepto r antagonistic activity.

3. Use of a CB_1 receptor antagonistic compound according to claim 1, wherein the use is in the manufacture of a medicament for the treatment and/or prophylaxis of obesity in juvenile patients and/or drug induced obesity in juvenile, as well as adolescent, patients.

4. Use of a CB_1 receptor antagonistic compound according to claim 1, wherein

the use is in the manufacture of a medicament for paediatric treatment and/or prophylaxis pertaining to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, neurological disorders such as dementia, distonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the paediatric treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the paediatric treatment of gastrointestinal disorders and cardiovascular disorders.

5. A pharmaceutical composition containing at least one CB_1 receptor antagonistic compound according to claim 1 or 2 as an active component for the treatment and/or prophylaxis of CB_1 receptor related diseases in juvenile patients and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, and at least one auxiliary excipient.

6. A pharmaceutical composition according to claim 5, wherein the at least one CB_1 receptor antagonistic compound is present in an amount effectively suited for the paediatric treatment and/or prophylaxis of a psychiatric disorder, a gastrointestinal disorder, a cardiovascular disorder, or a combination of said disorders, in a juvenile patient in need of such treating.

7. A pharmaceutical composition according to claim 5, wherein the at least one CB_1 receptor antagonistic compound of is present in an amount effectively suited for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients in need of such treating.

8. A method of treatment and/or prophylaxis of CB_1 receptor related diseases in juvenile patients (paediatric treating) and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, characterized in that a CB_1 receptor antagonistic compound accordi ng to claim 1 and/or 2 is administered to said patient in need of such treating.

9. A method of treatment and/or prophylaxis according to claim 8, characterized in that the paediatric treating is directed to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease,

Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission.

10. A method of treatment and/or prophylaxis according to claim 8, characterized in that the treating is directed to obesity in juvenile patients.

11. A method of treatment and/or prophylaxis according to claim 8, characterized in that the treating is directed to drug induced obesity in juvenile or adolescent patients.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/051976

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/435 A61K31/4164 A61K31/415 A61K31/4045 A61K31/397
A61K31/352 A61K31/05 A61P3/04 A61P25/18 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/007887 A (PLUMMER CHRISTOPHER W ;FINKE PAUL E (US); MERCK & CO INC (US); MIL) 30 January 2003 (2003-01-30) cited in the application page 30	1-11
X	US 2001/053788 A1 (TULP MARTINUS T M ET AL) 20 December 2001 (2001-12-20) cited in the application page 2, left-hand column, last paragraph - right-hand column, paragraph 3 claims 1,18-24	1-11
X	WO 03/051851 A (ASTRAZENECA UK LTD ;BERGGREN ANNA INGRID KRISTINA (SE); WILSTERMAN) 26 June 2003 (2003-06-26) cited in the application claims 1,10,13,15	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 344 474 B1 (MARUANI JEANNE ET AL) 5 February 2002 (2002-02-05) column 1, line 65 - column 2, line 58	1-3,5,8, 10
X	FR 2 814 678 A (AVENTIS PHARMA SA) 5 April 2002 (2002-04-05) cited in the application abstract claims	1-5,7-11
X	BARTH F: "Cannabinoid receptor agonists and antagonists" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 8, no. 3, March 1998 (1998-03), pages 301-313, XP002150850 ISSN: 1354-3776 the whole document	1-3,5-8, 10,11
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8-11
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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